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The prognostic value of histological grade on mortality/recurrence in early-stage ER+/HER2- BC patients: a systematic review

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ADMINISTRATIVE INFORMATION

Support - MSD China.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - Authors Jiali Wang and Liang Ding are employed by MSD China. Other authors report no conflict of interest.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 April 2025 and was last updated on 17 April 2025.

INTRODUCTION

Review question / Objective To summarize current evidence exploring impact of histologic grade on mortality and recurrence in stage II-III ER+/HER2- breast cancer patients and then to explore the prognostic value of histological grade (G3 vs. G1-2) on mortality and recurrence.

Rationale Identifying high risk pts will assist expansion of neoadjuvant/adjuvant (NAT/AT) pembrolizumab use in grade 3 (G3) ER+/HER2- population. Treatment strategy for ER+/HER2- BC patients is determined based on risk prognosis stratification. Different treatment modalities are administered based on different risk stratifications for recurrence/mortality. Immunotherapy as pembrolizumab (KEYNOTE-756) and nivolumab (CheckMate 7FL) showed significantly improvement in this population. The definition of G3 in breast cancer pathology refers to tumors that are classified as having a histological grade of three, which typically indicates poor differentiation of tumor cells and high proliferation activity. Data gap of the independent prognostic value of histological G3 on mortality/recurrence in early-stage ER+/HER2- patients, especially on event-free survival (EFS) and overall survival (OS), still remains. Although St. Gallen Consensus, the National Comprehensive Cancer Network (NCCN) guidelines and the American Society of Clinical Oncology (ASCO) guidelines consider G3 to be a high-risk factor, but not an independent high-risk prognostic indicator. However, AJCC (8th ed) cancer staging guidelines includes Grade in determining prognostic stage groupings for breast cancer. A US SEER cancer registry study in AJCC showed histologic grade as an important prognostic factor, independent of tumor size and number of positive lymph nodes(3). While ER+/HER2- BC patients with G3 might exhibit increased resilience to standard therapeutic approaches, including chemotherapy and hormonal treatments,

their responsiveness to these treatments can often be suboptimal. Therefore, the classification of G3 is significantly important in clinical decision-making and the choice of treatment regimens. To further enhance the integrated evidence on the prognostic role of histological grade on clinical outcomes especially on survival outcomes, it is meaningful to synthesize current available evidence to explore the mortality/recurrence in Stage II-III ER+/HER2- patients with G3. This will help us identify the value of applying NAT/AT pembrolizumab in G3 ER+/HER2- BC patients.

Condition being studied Breast cancer (BC) is a widespread global health challenge that has serious impacts on both illness and mortality rates(1) . Worldwide, female breast cancer has surpassed lung cancer as the most commonly diagnosed cancer, with an estimated 2.3 million new cases (11.7%)(1) . There are approximately 2.3 million new cases and 685,000 deaths from BC each year (2) .
Estrogen receptor positive (ER+)/human epidermal growth factor receptor 2 negative (HER2-) BC is a heterogeneous disease that includes a high-risk subgroup characterized by higher histological grade, resistance to endocrine therapy, heightened sensitivity to chemotherapy, and poor prognosis. In fact, high-risk early-stage ER+/HER2- BC clinically resembles triple-negative breast cancer (TNBC), leading to early recurrence and shortened survival. Therefore, it represents a field with a significant unmet medical need.

METHODS

Participant or population Stage II-III ER+/HER2- BC pts.

Intervention Histological grade (histological grade 3).

Comparator Histological grade (histological grade 1-2).

Study designs to be included Cohort studies, full text.

Eligibility criteria Inclusion criteria
Popultion: Stage II-III ER+/HER2- BC pts. ER+ is defined as positive for estrogen receptors (ER+), or both (ER/PR+). ER and PR are considered positive if the immune histochemistry (IHC) staining is positive in>=1% of tumor cells. HER2- indicates that the expression level of HER2 protein in tumor cells is low or absent, or that the HER2 gene is not amplified. There are absolutely no limitations or constraints whatsoever pertaining to age, race, treatments, or any other existing health conditions.
Intervention: Histological grade (histological grade 3).
Comparator: Histological grade (histological grade 1-2).
Outcomes: Primary Outcomes: EFS, OS, Distant Relapse-Free Survival(DRFS), Disease-free survival (DFS), invasive disease-free survival (iDFS) or Time to Recurrence (TTR). Secondary Outcomes: Pathological complete response (pCR). All outcome indicator definitions will be used according to the articles. If definitions of outcome indicators were different in articles, they will be analyzed separately. If the name of the outcomes does not match the definition, the definition has prevailed to determine the indicator. There is no time limit for follow-up, with a focus on long-term follow-up.
Time: No limitation.
Study design: Cohort studies. Full text.
Language: English.
Exclusion criteria
Population: 1) Patients with other cancers. 2) Not ER+/HER2- BC patients, such as TNBC, HER2+. 3) Patients with other stages
of breast cancer.
Intervention/Comparator: The factor was not histological grade.
Outcomes: Not reported any primary outcomes or secondary outcomes.
Study design: 1) Other study design. 2) Studies without available full text.
Language: other language.

Information sources PubMed/Medline, EMBASE, the Cochrane Library.

Main outcome(s) EFS, OS, Distant Relapse-Free Survival (DRFS), Disease-free survival (DFS), invasive disease-free survival (iDFS) or Time to Recurrence (TTR).

Additional outcome(s) Pathological complete response (pCR).

Data management All data collected for the study should be recorded accurately, promptly, and legibly. For primary data collection, the investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. For data not obtained from a primary source (i.e., secondary data, such as claims and electronic health records), the investigator is responsible for reviewing data quality and relevance to the best of the investigator's knowledge. By signing this protocol either electronically or written, the investigator confirms that the quality and relevance

of data has been assessed to meet the minimum requirements for all study objectives.

Quality assessment / Risk of bias analysis Two reviewers will independently assess the risk of bias of included studies, and the third party will be responsible for resolving the inconsistency. Cochrane Prognosis Methods Group recommends the use of the Quality In Prognosis Studies (QUIPS) tool to assess risk of bias (RoB) in prognostic factor studies.

Strategy of data synthesis All data will be extracted by two independent reviewers. Discrepancies will be resolved by consensus or by involving a third team member. Before data extraction begins, a standardized data extraction form/database and data extraction guidelines will be used following its review by the study statistician and upon achieving consensus by the study team on all included data fields. Data will be extracted from original research papers. Multiple reports of the same study will be collated and judged on the basis of population and diagnosis. If they had consistent population and diagnosis, we will only extract data from the one which was published more recently and had more sample size.

Subgroup analysis Provided that the extracted data is sufficient, a subgroup analysis will be executed based on the type of intervention (NAT vs AT vs NAT+AT), age categories (≤ 40 years vs > 40 years), and the menopausal status of the patients.

Sensitivity analysis Sensitivity Analyses is not applicable for this systematic review.

Language restriction English.

Country(ies) involved China.

Keywords Breast cancer; stage II-III; Histological grade; survival outcomes; pCR.

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